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Use of Amiodarone after Major Lung Resection

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Abstract

BACKGROUND—We evaluated the association of respiratory complications and amiodarone use in patients with atrial fibrillation (AF) after major lung resection.

METHODS—Outcomes of patients who had postoperative AF treated with or without amiodarone after lobectomy, bilobectomy, or pneumonectomy at a single institution between 2003 and 2010 were evaluated using multivariable logistic modeling.

RESULTS—Of 1412 patients who underwent lobectomy, bilobectomy, or pneumonectomy, AF occurred in 232 (16%). AF developed after a respiratory complication in 31 patients, who were excluded from subsequent analysis. The remaining 201 patients that had AF without an antecedent respiratory complication had similar mortality (3.0% [6/201] versus 2.5% [30/1180], $p=0.6$) and respiratory morbidity (10% [20/201] versus 9% [101/1180], $p=0.5$) but longer hospital stays (5 [4,7] versus 4 days [3,6], $p<0.0001$) compared to the 1180 patients that did not have AF. Amiodarone was used in 101 (50%) of these 201 patients, including 5 patients who had a pneumonectomy. Age, pulmonary function, and operative resection were similar between the patients treated with/without amiodarone. Amiodarone use was not associated with a significant difference in the incidence of subsequent respiratory complications [12% (12/101 amiodarone patients) versus 8% (8/100 non-amiodarone patients), $p=0.5$].

CONCLUSIONS—AF that occurs without an antecedent respiratory complication in patients after major lung resection results in longer hospital stay but not increased mortality or respiratory morbidity. Using amiodarone to treat atrial fibrillation after major lung resection is not associated with an increased incidence of respiratory complications.

Keywords

Atrial fibrillation; Lobectomy; Pneumonectomy; Outcomes

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Introduction

Supraventricular arrhythmias including atrial fibrillation, atrial flutter, and supraventricular tachycardia occur in up to 25% of patients after lung resections, most often on the second post-operative day [1–8]. Risk factors for arrhythmia include more extensive resections such as bilobectomy and pneumonectomy, intrapericardial and extrapleural pneumonectomy, right-sided procedures, age over 60, male gender, nonblack race, stage II or higher lung cancers, history of congestive heart failure, history of previous arrhythmia, preoperative heart rate greater than or equal to 72 beats per minute, history of peripheral vascular disease, intra-operative transfusions, and the occurrence of another complication [4–6,8–11]. The precise cause of arrhythmias after anatomic lung resections is unclear and likely multifactorial, involving hilar dissection, autonomic denervation, stress-mediated neurohumoral mechanisms, inflammatory mediators, and atrial size [5,8,12–14]. Postoperative arrhythmias are associated with a prolonged hospital stay, higher hospital costs, and increased mortality, as well as an increased occurrence of other complications [4,7,9,10,15–16].

Amiodarone is an antiarrhythmic agent commonly used to treat atrial fibrillation. Pulmonary toxicity, including chronic interstitial pneumonitis, organizing pneumonia, and adult respiratory distress syndrome (ARDS), occurs in approximately 5% of patients that receive amiodarone, with older age and higher amiodarone doses being risk factors [17,18]. The safety of using amiodarone after lung resection in general and pneumonectomy in particular was questioned by a prospective, randomized single center study that was evaluating the prophylactic use of amiodarone after lung resection and was terminated early when three of 11 patients who were given amiodarone after right pneumonectomy developed ARDS [19]. Despite this risk of pulmonary toxicity, amiodarone has been shown to be effective when given prophylactically for the prevention of atrial fibrillation after lung resection as well as to be safe when given to treat atrial fibrillation after lung resection [20–24]. However, these studies were all relatively small, with the largest study involving 65 patients who were given amiodarone after lung resection. The purpose of this study is to examine whether amiodarone administration after major lung resection is independently associated with pulmonary complications in a larger cohort of patients. The study tested the hypothesis that amiodarone, when used to treat atrial fibrillation that occurs after lobectomy, bilobectomy, or pneumonectomy, is independently associated with increased risk of pulmonary complications.

Patients and Methods

Local Institutional Review Board approval was granted for this study, including waiver of the need for patient consent. All patients treated with lobectomy, bilobectomy, or pneumonectomy from October 28, 2003 through October 1, 2010 were identified both by review of a prospectively maintained database of thoracic surgery patients at Duke University as well as by query of Duke University Health System electronic records using specific procedure codes associated with lobectomy, bilobectomy, and pneumonectomy. Patients that underwent extrapleural pneumonectomy for malignant mesothelioma were excluded from the analysis, as were patients who had concomitant chest wall or diaphragm resection or who were chronically in atrial fibrillation prior to surgery. Retrospective review

of the institutional, prospective thoracic surgery database documented demographics, preoperative functional status, use of induction therapy, smoking history, significant comorbidities, histology and disease stage, intraoperative details, and postoperative course. Chart review was utilized as necessary to complete data collection. Individual operative notes and surgical pathology reports to confirm that patients underwent anatomic lobectomy, bilobectomy, or pneumonectomy.

Postoperative amiodarone use was ascertained using the Duke University Health System DEDUCE tool that allows query of medication orders. The earliest data available for medications via this tool was October 28, 2003. The study therefore considered patients who had surgery between October 28, 2003 and October 1, 2010. Within this study timeframe, patients were not routinely given any prophylactic agents for atrial fibrillation.

Postoperatively, all patients had continuous telemetry monitoring. Atrial fibrillation suspected by telemetry was confirmed with 12-lead electrocardiograms. Atrial fibrillation treatment was provider dependent, and typically would involve beta-blockers, calcium-channel blockers, or amiodarone. The standard amiodarone regimen was initial intravenous bolus of 150 mg followed by continuous intravenous administration at 1 mg/min for 6 hours and then 0.5 mg/min for 18 hours, after which patients were converted to an oral daily dose of 200 mg. Duration of treatment was at the discretion of the surgeon, but the medication was usually discontinued no later than after 30 days of treatment if the patients were in sinus rhythm on follow-up. Patients who were taking rate-controlling agents such as beta-blockers and calcium-channel blockers before surgery had these medications routinely continued in the perioperative period. Anticoagulation was not typically used.

Outcomes of interest included any postoperative event prolonging or otherwise altering the postoperative course as well as operative deaths, which were defined as deaths that occurred within 30 days of the operation or prior to discharge. Deaths were captured both by chart review and use of the Social Security Death Index Database. The definitions of postoperative events were based on the Society of Thoracic Surgeons General Thoracic Surgery Database, and were clearly stated prior to data collection and assessed blinded to exposure variables [25]. Respiratory morbidity was defined as the occurrence of at least one of the following postoperative events: atelectasis requiring bronchoscopy, pneumonia, reintubation, and tracheostomy. These pulmonary complications were considered together because they all could be expected to occur more often in the setting of amiodarone-induced lung parenchymal injury.

The cohort used for the amiodarone risk analysis was assembled as follows (Figure 1). The patients were initially divided into two groups according to whether or not they had postoperative atrial fibrillation, and baseline characteristics, operative details, and postoperative outcomes between these two groups were evaluated with univariate analysis. In the cohort of patients that had postoperative atrial fibrillation, patients who had a respiratory complication that occurred before the onset of atrial fibrillation were excluded from the subsequent analysis that evaluated the risk of amiodarone use. This exclusion was done because the main objective of the study was to assess the risk of having a respiratory complication after amiodarone use. In the cohort of interest, baseline characteristics, operative details, and outcomes between patients that did/did not receive amiodarone were

compared. In addition, these variables were also compared between patients that did/did not receive amiodarone in a potentially higher risk subgroup of patients with poor pulmonary function, defined as either preoperative forced expiratory volume in one second (FEV1) or preoperative diffusion capacity of the lung to carbon monoxide (DLCO) less than 60% predicted.

Multivariable analysis of the patients who had atrial fibrillation that did not occur after a respiratory complication was performed to assess whether amiodarone exposure is an independent risk factor when other known risk factors for pulmonary complications are considered. The number of risk factors to consider in the model in addition to the risk factor of interest (amiodarone use) was chosen after review of the number of outcome events. The risk factors chosen for analysis were those previously shown to be strongly associated with respiratory complications in other studies: age, extent of resection (lobectomy, bilobectomy, sleeve lobectomy, pneumonectomy) and preoperative percent predicted DLCO. The model was created using stepwise selection with p-values of 0.1 both for entry into and to stay in the model. Because amiodarone exposure was the main predictor of interest, its inclusion was forced into the model.

The Mann-Whitney-Wilcoxon test was used to compare continuous variables, and conventional chi-square or Fisher's exact test was used to compare categorical variables. A nominal two-sided p-value of less than 0.05 was considered significant. Continuous data was presented as mean $\pm$ standard deviation or median (25th, 75th percentile). SAS V9.2 or higher (SAS Institute, Cary, North Carolina) was used for statistical analyses.

Results

Lobectomy, bilobectomy, and pneumonectomy were performed in 1412 patients overall during the study period. Table 1 shows the baseline characteristics, comorbid conditions pathologic cancer stage, and resection details for patients stratified by whether or not they developed atrial fibrillation. Two lobes were resected in 72 of the lobar resections; 31 of these procedures were done via VATS and 41 were done via thoracotomy. Of the lobar resections, 69 were sleeve resections. Table 2 shows post-operative events and outcomes. Overall mortality was 3.2% (46 patients) and overall morbidity was 40% (558 patients).

Atrial fibrillation was the most common complication, and occurred in 232 patients (16%). As shown in table 1, patients that developed atrial fibrillation were older, had lower percent predicted FEV1 and DLCO, and more often had hypertension, coronary artery disease, and thoracotomy as the surgical approach for lobar resections when compared to patients that did not have atrial fibrillation. The occurrence of atrial fibrillation was associated with longer hospital stay and significantly increased mortality. Atrial fibrillation was also associated with an increased incidence of other complications, including post-operative transfusion, any respiratory complication, prolonged air leak, need for an enteral feeding tube, new renal insufficiency, and reoperation for bleeding (Table 2).

Respiratory complications also occurred in 22% (n=51) of the 232 patients that had atrial fibrillation. Overall outcomes were significantly different depending on the timing of atrial

fibrillation and respiratory complications. Atrial fibrillation developed after a respiratory complication had already occurred in 31 of these patients (13%). These 31 patients had a perioperative mortality of 32% (10 patients) and a median hospital stay of 14 days (9,31). The remaining 201 patients that had atrial fibrillation had a perioperative mortality of 3.0% (n=6) and median hospital stay of 5 days (4,7), both of which were significantly less than those of the patients who developed atrial fibrillation after a respiratory complication ($p<0.0001$ and $p<0.0001$, respectively). These 201 patients who had atrial fibrillation that did not occur after a respiratory complication had similar perioperative mortality [3.0% (6 of 201) versus 2.5% (30 of 1180), $p=0.6$] but longer hospital stays [5 days (4,7) versus 4 days (3,6), $p<0.0001$] when compared to the 1180 patients that did not have atrial fibrillation.

Of the 201 patients who had atrial fibrillation that did not occur after a respiratory complication, 10% (n=20) had a subsequent respiratory complication that occurred after initially having atrial fibrillation. Amiodarone was used in 101 (50%) of these 201 patients; pre-operative medications in these 101 patients included a beta-blocker in 33 (33%) and a calcium-channel blocker in two (2%). Amiodarone was administered in the hospital only in 35 patients (35%), while 66 patients (65%) were discharged on an oral short-term regimen of amiodarone. Of the 101 patients that were given amiodarone, other medications that were given prior to amiodarone administration and failed to adequately control post-operative atrial fibrillation included intravenous diltiazem (n=9, 9%) and an intravenous beta-blocker (n=67, 66%). Of the patients that were given amiodarone, 97% (98 of 101) were in sinus rhythm at the time of discharge and 90 of 92 (98%) patients who had rhythm recorded at the first post-discharge follow-up visit were in sinus rhythm. There were 19 patients treated with amiodarone who had a readmission after their initial hospitalization, two of whom were admitted for management of recurrent atrial arrhythmias. The other reasons for readmission were management of dyspnea (n=3), pneumonia (n=3), wound complication (n=3), pulmonary embolus (n=2), pneumothorax (n=2), pulmonary secretion management (n=1), and pleural effusion (n=3).

Patients that received amiodarone had similar ages, pre-operative pulmonary function, extent of resection, and operative approach when compared to patients that were not given amiodarone, though patients who received amiodarone were more likely to have had previous thoracic surgery (Table 3). Outcomes in terms of 30-day mortality, hospital stay, and both aggregated and individual respiratory complications were not significantly different between the patients that were given and not given amiodarone. In univariate analysis, amiodarone use was not associated with a significant difference in the incidence of subsequent respiratory complications [12% (12 of 101 patients that received amiodarone) versus 8% (8 of 100 patients that were not given amiodarone), $p=0.5$]. In a multivariate model that included amiodarone use as well as other known risk factors for respiratory complications, percent predicted DLCO was the only statistically significant predictor of respiratory complications (Table 4). In subgroup analysis of patients with poor pulmonary function who had atrial fibrillation after lobectomy, bilobectomy, or pneumonectomy, amiodarone use was also not significantly associated with perioperative mortality or respiratory morbidity (Table 5).

Comment

In this study, we found that atrial fibrillation was the most common postoperative complication that occurred in a cohort of patients who underwent lobectomy, bilobectomy, or pneumonectomy. The occurrence of atrial fibrillation was associated with significantly increased mortality, longer hospital stay, and an increased incidence of other complications, including respiratory complications. Amiodarone was not associated with an increased risk of respiratory complications when used to treat atrial fibrillation in patients that had not already suffered a respiratory complication. Despite the efficacy of amiodarone in treating atrial fibrillation, some surgeons have been reluctant to use amiodarone after major lung resection due to both its known association with pulmonary toxicity as well as previous reports that have suggested amiodarone use increases the risk of pulmonary complications after lung resection [19]. This study that includes 101 patients treated with amiodarone after major lung resection suggests that amiodarone is indeed safe to use in this setting.

The finding that patients with atrial fibrillation had significantly worse mortality than patients who did not have atrial fibrillation is similar to what has been shown by previous studies [8]. However, more detailed analysis in our study shows there are two different subsets of patients in regards to the association of atrial fibrillation and other outcomes. Patients who develop atrial fibrillation after already having had a respiratory complication had significantly increased mortality and hospital stays when compared to patients who develop atrial fibrillation without already having had a respiratory complication. The impact on ultimate outcomes of developing atrial fibrillation after another serious complication is unclear. However, patients who develop atrial fibrillation without already having had a respiratory complication have similar mortality but longer hospital stays compared to patients who do not have postoperative atrial fibrillation. Therefore, strategies that prevent or more quickly treat atrial fibrillation after major lung resection have the potential to reduce costs by reducing hospital stay.

The main strength of this study is that the sample size of patients treated with amiodarone is larger than other published studies that have investigated the use of amiodarone after lung resection. This sample size allowed creation of a multivariable model of complications using previously published prognostic factors in addition to amiodarone use. A limitation of this proposed study is its at least partial reliance on an administrative database regarding amiodarone use. Amiodarone may have been ordered but not given to some patients, and therefore the effect of amiodarone use may be incorrectly calculated. However, this scenario is felt to be uncommon and therefore its effect on the study findings is expected to be small. Another limitation is that the total amount of amiodarone given to patients cannot be calculated, and therefore a dose effect cannot be evaluated and is beyond the scope of the study. Pharmacy records can be used to calculate the inpatient amiodarone doses, but the dose and duration of amiodarone given to patients after discharge in this clinical situation varies considerably and generally cannot be accurately determined via medical record review.

Other limitations of this study are the retrospective nature and the fact that only patients at a single institution were examined. Although the treatment of all patients who develop

postoperative atrial fibrillation at our institution follows a general pathway, not all patients are treated by the same providers or in precisely the same manner. This limitation introduces potential confounders such as different selection criteria for amiodarone use amongst the patients examined. Although the patients who did and did not get amiodarone were well balanced in terms of the most significant risk factors for respiratory complications (age, surgical extent, pulmonary function), the results could have been biased by other unmeasured confounders related to amiodarone use. In addition, including a heterogeneous group of patients in the cohort increases the statistical power of the study but does limit the ability to directly apply the results to a specific patient population, although the analysis did attempt to control for the heterogeneity in the multivariable model. The study is also limited to evaluating amiodarone's safety but not efficacy as compared to other treatment strategies, as the use of amiodarone in the majority of patients was after other treatment strategies had failed. Finally, this study does not allow comment on the safety of using amiodarone after a patient has already had a respiratory complication. Caution must be used in these patients who likely already have injured lung parenchyma, as they may be both more susceptible to further injury as well as more likely to show significant clinical deterioration from any further injuries.

In conclusion, atrial fibrillation is a common occurrence after major lung resection. This complication leads to longer hospitalizations and likely increased costs. Amiodarone is very effective at treating atrial fibrillation but is known to cause pulmonary toxicity. Although the safety of using amiodarone in the setting of major lung setting has previously been questioned, amiodarone use in this study was not associated with increased respiratory complications.

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Figure 1.

Cohort assembly of the patients included in amiodarone risk analysis.

Table 1

Baseline characteristics and operative details for all patients.

Characteristic	Atrial Fibrillation (n=232)	No Atrial Fibrillation (n=1180)	p
Median Age (range)	69 (45–89)	64 (13–>89)	<0.0001
Forced Expiratory Volume in one second (% predicted)	69±20	74±20	0.0004
Diffusing Capacity of the Lung for Carbon Monoxide (% predicted)	74±21	77±21	0.01
Previous Thoracic Surgery	54 (23%)	244 (19%)	0.4
Pre-operative Chemotherapy	41 (18%)	190 (16%)	0.6
Pre-operative Radiation	27 (12%)	131 (11%)	0.8
Hypertension	139 (60%)	574 (49%)	0.002
Cerebrovascular Disease	13 (6%)	88 (7%)	0.4
Coronary Artery Disease	54 (23%)	194 (16%)	0.01
Diabetes	41 (18%)	195 (16%)	0.7
Peripheral Vascular Disease	18 (8%)	71 (6%)	0.3
Renal Insufficiency	15 (6%)	49 (4%)	0.1
Congestive Heart Failure	9 (4%)	37 (3%)	0.5
Pathology			0.07
Benign	19 (8%)	147 (12%)	
Malignant	213 (92%)	1033 (88%)	
Resection			
Lobectomy/Bilobectomy	207 (89%)	1098 (93%)	0.06
Thoracotomy	80 (39%)	330 (30%)	0.02
Thoracoscopy	127 (61%)	768 (70%)	
Pneumonectomy	25 (11%)	82 (7%)	
Thoracotomy	25 (100%)	79 (96%)	1
Thoracoscopy	0 (0%)	3 (4%)	

Table 2

Postoperative events.

Event	Atrial Fibrillation (n=232)	No Atrial Fibrillation (n=1180)	p
Thirty-day Mortality	16 (6.9%)	30 (2.5%)	0.002
Hospital Stay (median)	6 (5,8)	4 (3,6)	<0.0001
Post-operative transfusion	39 (17%)	103 (9%)	0.0005
Any Pulmonary Complication	51 (22%)	101 (9%)	<0.0001
Need for chest tube > 5 days	39 (17%)	122 (10%)	0.006
Post-operative bronchoscopy	45 (19%)	75 (6%)	<0.0001
Pneumonia	23 (10%)	41 (3%)	<0.0001
Need for enteral nutrition tube	13 (6%)	28 (2%)	0.02
Unplanned reintubation	17 (7%)	27 (2%)	0.0003
Delirium/Mental Status Changes	7 (3%)	24 (2%)	0.3
New Renal Insufficiency	12 (5%)	17 (1%)	0.001
Wound Infection/Empyema	6 (3%)	15 (1%)	0.1
Need for tracheostomy	9 (4%)	16 (1%)	0.01
Re-operation for bleeding	6 (3%)	11 (1%)	0.05
Vocal cord paralysis	4 (2%)	15 (1%)	0.5
Re-operation for decortication	3 (1%)	7 (1%)	0.2
Myocardial infarction	1 (0.4%)	4 (0.3%)	0.6
Pulmonary embolism	0	4 (0.3%)	0.5

Table 3

Amiodarone use in patients with atrial fibrillation prior to or in the absence of a respiratory complication.

	Amiodarone Used (n=101)	Amiodarone Not Used (n=100)	p
Median Age (range)	69 (46–89)	69 (45–86)	1
Diffusing Capacity of the Lung for Carbon Monoxide (% predicted)	73±21	77±21	0.3
Forced Expiratory Volume in one second (% predicted)	69±20	73±20	0.1
Previous Thoracic Surgery	30 (30%)	14 (14%)	0.01
Resection			
Lobectomy	96 (95%)	88 (88%)	0.08*
Thoracoscopy	61 (64%)	56 (64%)	
Thoracotomy	35 (36%)	32 (36%)	
Pneumonectomy	5 (5%)	12 (12%)	
30-day Mortality	3 (2.9%)	3 (3%)	1
Hospital Stay	6 (5,7)	5 (4,7)	0.08
Any Respiratory Complication	12 (12%)	8 (8%)	0.5
Bronchoscopy	11 (11%)	5 (5%)	0.2
Pneumonia	3 (3%)	2 (2%)	1
Re-Intubation	2 (2%)	2 (2%)	1
Tracheostomy	1 (1%)	1 (1%)	1

* p-value for lobectomy/bilobectomy versus pneumonectomy for patients with and without atrial fibrillation

Table 4
Logistic regression model of risk factors for developing respiratory complications after the occurrence of atrial fibrillation.

Variable	Univariate			Multivariate		
	Odds Ratio	95% CI	p	Odds Ratio	95% CI	p
% predicted Diffusing Capacity of the Lung for Carbon Monoxide (per 10 point decrease)	1.27	0.99–1.63	0.06	1.29	1.00–1.67	0.047
Amiodarone	1.55	0.60–3.97	0.4	2.10	0.72–6.17	0.2
Age						
Extent of Surgery	0.96	0.90–1.01	0.09	0.94	0.89–1.00	0.06

CI = Confidence Interval

Table 5

Atrial fibrillation and amiodarone use for patients with impaired pulmonary function.

	Amiodarone Used (n=54)	Amiodarone Not Used (n=46)	p
Median Age (range)	69.5 (66–75)	70 (64–75)	0.6
Diffusing Capacity of the Lung for Carbon Monoxide (% predicted)	59±17	59±12	0.4
Forced Expiratory Volume in one second (% predicted)	55±15	60±20	0.2
Resection			0.3
Lobectomy	51 (94%)	40 (87%)	
Pneumonectomy	3 (6%)	6 (13%)	
30-day Mortality	1 (2%)	3 (6%)	0.3
Hospital Stay	7 (5,8)	5 (4,9)	0.2
Any Respiratory Complication	10 (19%)	5 (11%)	0.4
Bronchoscopy	9 (17%)	2 (4%)	0.06
Pneumonia	3 (6%)	2 (4%)	1
Re-Intubation	2 (4%)	2 (4%)	1
Tracheostomy	1 (2%)	1 (2%)	1